

FACTORS INFLUENCING THE AGE AT NATURAL MENOPAUSE

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Abstract—To examine sociodemographic, menstrual, reproductive, and other factors which may influence the age at natural menopause, the authors analyzed data from a large series of women participating in a nationwide breast cancer screening program conducted between 1973 and 1980. Standard life table techniques permitted assessment of factors suspected of varying the time to menstrual cessation among 983 premenopausal women, 1091 surgically menopausal women, and 1423 naturally menopausal women. The median age at natural menopause was 51.1 years. Multivariate analysis indicated that parity, irregularity of menstrual cycles before age 25 or first livebirth, and high socioeconomic status were significantly related to menopausal age. These data provide evidence for the hypothesis that certain environmental and hormonal factors which affect ovulation during reproductive years may ultimately postpone the menopause.

Menopause Menopausal age Risk Environmental factors Epidemiology

INTRODUCTION

A recent review of data on natural menopause noted the prevailing view that menopause results from peripheral organ failure, namely of the ovaries, but that the mechanisms and the role of the pituitary gland remain unknown [1]. The median age of menopause, 50 years, has not changed over the last century according to some reports [2-4]. Although this would appear to support the notion that age at menopause is predetermined, a number of environmental factors have been shown to affect ovarian function. Smoking [5-8], obesity [3, 9], parity [3, 4, 10], age at menarche [3, 10], oral contraceptive use [11], race [3, 12] and sociodemographic factors [3, 7, 11] have been studied in relation to menopausal age, but some findings have not been consistent or confirmed. Factors delaying menopause may have important clinical implications since they may postpone development of postmenopausal medical conditions such as cardio-

vascular disorders and osteoporosis, but may increase the risk of endometrial and breast cancer. We therefore studied the independent effects of variables that may influence a woman's age at natural menopause and the interrelationships among these factors in a cross sectional epidemiologic analysis.

METHOD

Study subjects were selected from participants in the Breast Cancer Detection Demonstration Project (BCDDP), a multicenter breast cancer screening program. In order to address a number of etiologic hypotheses, a case-control study was conducted among women whose breast cancer was diagnosed during July 1973 through May 1977. An extension of the study (through November 1980) permitted ascertainment of additional cases and collection of data on smoking status, which was not recorded in the original questionnaire. For this reason, the analysis of smoking variables was limited to women participating in the latter 3 years of the screening program. A large number of non-hospitalized, community-based women who volunteered for

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participation in the screening project formed the pool from which control subjects were randomly selected. Controls were stratified to cases on screening center, age (within 5 years), race, time of entry, and length of continuation in the screening program. Controls were women who had no previous history of breast cancer and who did not receive either a recommendation for biopsy or a breast biopsy during the course of the screening project. Methods for this study have been previously described in detail [13]. The present analysis included only the control subjects.

Standardized personal interviews were conducted by trained interviewers. Completed interviews were obtained on 83% of the 4279 eligible controls. Major reasons for nonresponse included refusals (7.8%), having moved from the study area (3.2%), and death of the study subject (2.3%).

The 3545 control women who completed detailed study interviews were classified according to menstrual status: premenopausal (28%), natural menopause (40%), surgical menopause (31%), and unknown menstrual status (1%). The month and year of a woman's last menstrual period were recorded, and a woman was considered naturally menopausal if the interval since last menses was >3 months. Ninety-five percent of the women who were categorized as naturally menopausal (1352 of 1423 women) had not had a menstrual period for >12 months, and 99% had not menstruated for ≥ 6 months. For menopausal study subjects, oral contraceptive and menopausal hormone exposure information were truncated to the date of menopause. Controls were excluded from the present analysis if they had unknown menstrual status (45), or reported natural or surgical menopause before age 20 (3). The final study group comprised 983 premenopausal, 1091 surgically menopausal, and 1423 naturally menopausal women.

A standard life table approach was used to accumulate the experience of both premenopausal women as well as surgically and naturally menopausal women [14]. Premenopausal women and those who had surgical menopause were treated as censored observations and were withdrawn from the analysis at the date of interview or date of hysterectomy, respectively. Median age at natural menopause was calculated according to a number of variables suspected of varying the time to menstrual cessation. Individual factors in the univariate

analysis which demonstrated >6 months difference in median age of menopause were further evaluated in a multivariate model. To examine the association of a variable with age at menopause while controlling for the effects of other factors, multivariate analysis was performed using a stepwise proportional hazards regression model [15]. Time-dependent covariates were created to evaluate some exposures, such as age at first livebirth and oral contraceptive use. The creation of time-dependent variables allows adjustment for the time at which an exposure occurs in relation to the outcome of interest. For example, in our study, non-users of oral contraceptives comprised women who willingly chose not to take these preparations as well as women who were not at risk for the exposure by virtue of having already experienced menopause prior to the availability of oral contraceptives, i.e. before 1960. In univariate analyses, oral contraceptives are considered as a fixed exposure, ever vs never use, with groups of unexposed women described above included in the never use category. Multivariate analyses incorporating time-dependent functions permit adjustment for the time at which a women first used oral contraceptives in relation to time of menopause, and adjusts for the fact that some non-users were not at risk for the exposure.

RESULTS

The age distribution of the 3497 study subjects according to menstrual status is presented in Table 1. The age range for experiencing natural menopause was 26–62 years. Figure 1 shows the percent of women having natural menopause by age, based on the cumulative experience of all study subjects. Median age at natural menopause estimated from this analysis was 51.1 years.

A number of variables that might influence menopausal age were examined. No consistent relationships were noted with race, age at menarche, age at first livebirth, history of breast feeding, family history of breast cancer (any first degree relative), height, weight, Quetelet index, or smoking (Table 2).

Several variables, however, were found to affect median age at natural menopause (Table 3). Demographic factors related to age at menopause included geographic area, income, education, and marital status. On average, women from the North Central and Southern study

Table 1. The age distribution of 983 premenopausal, 1091 surgically postmenopausal, and 1423 naturally postmenopausal study subjects

Age* (yr)	Premenopausal		Surgical menopause		Natural menopause	
	No.	%	No.	%	No.	%
22			1	0.09		
23			2	0.28		
24			1	0.09		
25			5	0.46		
26			4	0.37	2	0.14
27			7	0.64	1	0.07
28			9	0.82		
29			10	0.92	4	0.28
30	1	0.10	10	0.92		
31	1	0.10	21	1.92	3	0.21
32	1	0.10	16	1.47	3	0.21
33			22	2.02	2	0.14
34	3	0.31	33	3.02	1	0.07
35	8	0.81	28	2.57	7	0.49
36	12	1.22	34	3.12	7	0.49
37	23	2.34	61	5.59	13	0.91
38	22	2.24	53	4.86	8	0.56
39	34	3.46	55	5.04	11	0.77
40	56	5.70	69	6.32	22	1.55
41	40	4.07	44	4.03	24	1.69
42	50	5.09	57	5.22	31	2.18
43	46	4.68	74	6.78	38	2.67
44	66	6.71	58	5.32	48	3.37
45	64	6.51	61	5.59	92	6.47
46	80	8.14	58	5.32	64	4.50
47	85	8.65	58	5.32	86	6.04
48	78	7.94	50	4.58	120	8.43
49	61	6.21	36	3.30	112	7.87
50	77	7.83	35	3.21	164	11.53
51	52	5.29	33	3.02	144	10.12
52	40	4.07	30	2.75	136	9.56
53	26	2.65	21	1.92	72	5.06
54	18	1.83	11	1.01	67	4.71
55	15	1.53	10	0.92	67	4.71
56	12	1.22	6	0.55	39	2.74
57	3	0.31	4	0.37	16	1.12
58	4	0.41	1	0.09	13	0.91
59	2	0.20	3	0.27	3	0.21
60	2	0.20			2	0.14
61						
62	1	0.10			1	0.07
Total	983	100%	1091	100%	1423	100%

*Age at censoring for premenopausal women, age at surgical or natural menopause for postmenopausal women.

centers reported earlier menopause than women from the West or North East. Low socioeconomic status, as measured by income or

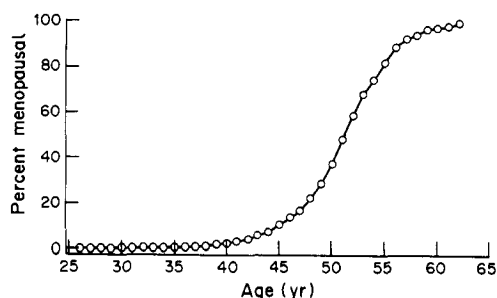


Fig. 1. Cumulative proportion of women experiencing natural menopause by age.

education, was related to earlier cessation of menstruation. Single women were younger at the time of menopause than women who had ever been married. Several menstrual and reproductive factors were related to age at menopause, including regularity of menses and parity. Women who reported regular menstrual periods before age 25 or first livebirth reached menopause 22.9 months before those with irregular periods during this time. Nulliparous women reached menopause 17.9 months earlier than parous women, and age at menopause was directly related to the number of livebirths.

Exogenous hormones, including prior use of oral contraceptives (OC) and menopausal es-

Table 2. Median age at natural menopause according to selected characteristics not found to be related to menopausal age

Variable	No. premenopausal (<i>N</i> = 983)	No. surgical menopause (<i>N</i> = 1091)	No. natural menopause (<i>N</i> = 1423)	Median age at natural menopause		<i>p</i> -value*
				Years	Months	
Race						
White	900	983	1347	51	3	0.71
Black	40	75	31	50	11	
Other	39	30	40	50	7	
Age at menarche (yr)						
≤ 11	186	164	208	51	5	0.16
12	253	269	299	51	5	
13	300	330	453	50	10	
≥ 14	241	324	458	51	8	
Age at first livebirth (yr)†						
≤ 24	560	587	538	51	5	0.20 (0.46)‡
25–29	242	261	387	51	7	
≥ 30	78	93	220	50	10	
Ever breast fed†						
No	399	329	403	51	4	0.55
Yes	482	612	744	51	5	
Family history of breast cancer						
No	870	939	1216	51	2	0.42
Yes	112	151	202	51	2	
Height (in.)						
≤ 64	543	638	895	51	1	0.61
≥ 65	426	473	514	51	3	
Weight (lb.)						
≤ 139	561	552	754	51	1	0.91
140–160	259	299	407	51	1	
≥ 161	152	224	249	51	4	
Quetelet index						
≤ 19	88	77	76	50	8	0.22
20–21	240	215	289	50	12	
22–24	342	349	488	51	4	
≥ 25	299	434	555	51	2	
Ever smoke cigarettes						
No	302	401	518	51	2	0.86
Yes	274	271	378	50	10	

*Mantel-Cox test for differences between groups specified.

†Analysis limited to parous women.

‡Age at first livebirth entered as a time-dependent covariate.

Analysis excludes unknowns.

trogens, were also related to age at menopause in the univariate analyses (Table 4). Women who had ever used OCs ceased menstruating about 10 months later than nonusers. This OC effect, however, became nonsignificant after accounting for the time of exposure ($p = 0.094$). Age at first use of OCs did not influence age at menopause (not shown). As expected, the use of menopausal estrogens was related to later menopause (about 18 months difference for never compared to ever use); menopausal age increased according to the duration of non-contraceptive estrogen use.

Several of the factors associated with age at

menopause were related to each other. Regression coefficients for variables that were independent significant predictors of the age at which a woman's menstrual cycling ended are shown in Table 5. The initial model included terms for all factors found to affect the age of menopause in the univariate analysis: geographic area, marital status, income, education, history of irregular menstrual periods, parity, and ever use of oral contraceptives. Because of the strong relationship between menopausal estrogen use and the outcome of interest, this variable was not incorporated in the model. Following a stepdown procedure, the important

Table 3. Median age at natural menopause according to selected characteristics found to be related to menopausal age

Variable	No. premenopausal (N = 983)	No. surgical menopause (N = 1091)	No. natural menopause (N = 1423)	Median age at natural menopause		p-value*
				Years	Months	
Geographic area						
West	264	379	414	51	6	0.02
N. Central	186	180	302	50	9	
N. East	213	146	255	51	3	
South	320	386	452	50	10	
Income						
≤\$9999	50	187	344	50	7	0.0001
10–19,999	188	261	350	50	11	
20–29,999	252	228	250	51	2	
≥\$30,000	402	286	285	51	10	
Education (yr)						
≤11	60	228	272	50	3	0.0003
12	397	379	534	51	4	
≥13	525	481	616	51	5	
Marital status						
Never married	43	26	74	50	1	0.0017
Ever married	939	1062	1345	51	2	
Menstrual periods						
Regular	812	912	1264	50	11	0.0001
Irregular	116	75	87	52	10	
Ever had a livebirth						
No	102	150	275	49	11	<0.0001
Yes	881	941	1147	51	5	
Number of livebirths						
0	102	150	275	49	11	<0.0001
1–2	375	470	645	50	11	
3–4	408	376	390	51	8	
≥5	98	95	112	51	11	

*Mantel-Cox test for differences between groups specified.

Analysis excludes unknowns.

Table 4. Median age at natural menopause according to exogenous hormone use

Variable	No. premenopausal (N = 983)	No. surgical menopause (N = 1091)	No. natural menopause (N = 1423)	Median age at natural menopause		p-value*
				Years	Months	
Ever used oral contraceptives						
No	574	890	1262	50	11	<0.0001
Yes	407	199	161	51	9	
						(0.094)†
Duration of use of oral contraceptives (yr)						
≤1	149	103	70	51	6	0.0002
2–4	90	35	44	51	9	
≥5	161	55	44	52	2	
						(0.062)†
Ever used menopausal estrogens						
No	885	1010	1213	50	10	<0.0001
Yes	96	74	202	52	4	
Duration of use of menopausal estrogens (yr)						
≤1	48	30	91	51	10	<0.0001
2–4	18	24	48	52	3	
≥5	27	17	59	53	10	

*Mantel-Cox test for differences between groups specified.

†Oral contraceptive use entered as a time-dependent covariate.

Analysis excludes unknowns.

Table 5. Proportional hazards regression coefficients for the association between selected covariates and age at natural menopause

Covariates	Categories	Unadjusted* regression coefficient β	Adjusted† regression coefficient β	<i>p</i> -value for adjusted β
Number of livebirths	Continuous (0–14)	–0.0887	–0.0722	0.0001
Menstrual cycles	Regular/irregular	–0.4273	–0.4199	0.0001
Income	0–3	–0.1192	–0.0826	0.003
Education	<12/≥12 years	–0.2562	–0.1628	0.045

*Model includes each covariate unadjusted for other covariates.

†Model includes number of livebirths, menstrual cycles, income and education.

‡Annual household income categorized as 0 ≤ \$10,000, 1 = \$10–19,999, 2 = \$20–29,999, 3 ≥ \$30,000.

predictive variables in order of relative significance were number of livebirths, regularity of menstrual periods, income, and education. Adjustment for year of birth, age at menarche, or menopausal estrogen use did not materially change these results.

DISCUSSION

In the present study, we have attempted to examine the effects of sociodemographic, physiologic, and pharmacologic variables on age at natural menopause employing life table and multivariate approaches in a large series of non-hospitalized women. Before discussing results, some attention should be given to methodologic issues. Concerns arise from the use of cross sectional data to estimate age of menopause. Specifically, memory bias may affect results as older women may not accurately recall the time of last menstruation [2, 16]. Another potential limitation of the study relates to the generalizability of findings, since women in the present analysis were self-selected for participation in the screening program.

In several previous studies another potential bias stems from the exclusion of women who had surgical menopause. Krailo and Pike [17] have suggested that estimates derived from prevalence data do not differ markedly from what would be expected based on a competing risks model which accounts for the influence of surgical menopause on the distribution of age at natural menopause. Based on our data, excluding women who had experienced surgical menopause (instead of including them as censored observations) would underestimate the median age at natural menopause by about 7 months. Considering surgically menopausal women as censored observations, however, assumes that their age at natural menopause in the absence of

surgery would have been similar to women without surgical intervention. It is not possible to verify that the reasons for censoring (hysterectomy) were independent from the outcome event (natural menopause), nonetheless we believe that inclusion of the surgical group in these analyses probably produced less biased estimates of menopausal age. Predictors of natural menopause, however, did not change substantially between analyses including compared to analyses excluding the surgery group.

Estimates of the age at natural menopause have remained constant over time according to some reports [2, 4], arguing that the onset of menopause is biologically predetermined by age. Alternatively, this invariance may reflect the net influences of contradictory forces, e.g. decreasing parity vs increasing OC use. Given these considerations, it is of interest that our data suggest that certain factors which affect ovulation over the reproductive life-span may delay the cessation of normal menstrual periods. Findings indicate the number of livebirths, a history of menstrual cycle irregularity, higher income (≥\$30,000) or higher education (≥12 years) may postpone the menopause. Several of these observations have been made previously, but the interdependence of effects has been unclear.

Parity was a significant independent predictor of menopausal age. Some previous studies have shown no relationship [7, 10]. However, our results are in agreement with several earlier studies that found nulliparous women to have earlier menopause than parous women [11, 18, 19]. The plausibility of the association is strengthened by the consistent trend with the number of children borne ($p = 0.0001$). Soberon *et al.* [19] also reported an increase in menopausal age with increasing numbers of

children, but other investigators found no evidence for a dose-response relationship [3, 7]. Age at menopause did not vary consistently by age at first livebirth or history of breast feeding. One possible explanation is that each pregnancy contributes by prolonging the duration of anovulatory ovarian cycles and that timing of the pregnancies is irrelevant.

Multivariate analysis also showed that a history of irregular menstrual cycles before age 25 years or first birth was an important predictor of time to menstruation cessation ($p = 0.0001$), that is, the absence of regular menstrual periods early in life was indicative of a woman's experience in later reproductive life. The correlation of irregular menses with anovulatory cycles may explain this result.

The relationship of oral contraceptive use and age of menopause has been previously examined in one study noting that long duration of OC use (25 + months) delayed menopausal age [11]. We found that ever use of OCs as well as duration of OC use were positively related to age at last menstrual period in the univariate life table analysis. Because women in the present study were older when OCs became available in the United States, we were concerned about the possible temporal aspects of OC usage. Further analysis of OCs as a time-dependent covariate were performed, and the OC effects became nonsignificant. These results highlight the importance of considering OCs as a time-dependent exposure. One explanation for the difference in findings is that women who never used OCs comprised those individuals who willingly chose not to use OCs and those who did not use OCs because they had already experienced natural menopause. In the multivariate analysis, the OC effect did not persist. Use of menopausal estrogens was also related to menopausal age, but we could not accurately assess the effect since these preparations were predominantly used during the perimenopause.

Our finding that lower income and less education were associated with earlier menopause is consistent with the findings from other studies [3, 7], but not with the work of Brand and Leherter [10] and van Keep *et al.* [11], who found no effect. Multivariate analysis suggested that income was a more important determinant than years of education, yet both were significant. Differences in nutritional status and other lifestyle practices not measured in our study may explain the relationships between menopausal age and sociodemographic factors. We had no

dietary data available to assess this issue. However, similar to other reports [10, 11], age of menopause did not vary consistently with height, weight, or Quetelet index. Several investigations noted a tendency for heavier women to have delayed menopause [3, 9, 20], but analyses may have been confounded by parity.

Race was not significantly related to menopausal age in our data, but black women reached menopause about 4 months earlier than white women. MacMahon and Worcester reported that the mean age at natural menopause was 0.7 years earlier for black compared to white women, although the difference was nonsignificant [3]. Another recent investigation [12] also found no black-white differences with regard to age of menopause. Findings related to geographic area contrast with an earlier report [3]. MacMahon and Worcester [3] reported no variation in menopausal age by geographic region, yet they did indicate that women residing in urban areas have delayed menopause compared to rural areas. Similar to other studies [3, 7], we found that single women experienced earlier menopause than married women. However, this relationship did not persist after adjustment for parity and prior OC use.

The lack of a relationship between smoking and menopausal age in our data is inconsistent with prior studies indicating a 1–2 year earlier menopause among smokers compared to nonsmokers [5–8, 21–23]. More refined analyses of menopausal age according to duration (total years smoked) and dose (number of cigarettes per day) of smoking also failed to demonstrate any differences (not shown). Reasons for this discrepancy are unclear, but it is noteworthy that studies of non-hospitalized women find less of an effect of smoking on menopausal age than those which include diseased subjects [13].

In summary, this study systematically attempts to disentangle the factors which influence the timing of natural menopause. Multivariate analyses indicate that parity, regularity of menstrual periods, income and education are important predictors of the end of menstrual activity. The data provide evidence that women whose ovaries are anovulatory during reproductive years may experience delayed menopause, although the precise mechanisms are unclear. This could be in accord with the notion that exhaustion of available follicles causes natural menopause. If anovulation is the mechanism whereby irregular periods early in re-

productive life and parity produce a delay in the age at menopause, one would expect that OC use would also postpone menopause. Since this cohort was dominated by women who were at older ages when OCs became available, our data did not provide an optimal situation for evaluating OC effects. Additional research on the relationship between menopausal age and factors associated with anovulatory menstrual cycles during reproductive years seems warranted. Furthermore, the present analysis highlights two complicated methodologic topics: (1) differences in estimates of median age at menopause may result if the experience of premenopausal and surgically menopausal women are not accounted for in the analysis, and (2) dissimilar findings may occur when evaluating exposures with fixed compared to time-dependent functions. Future studies assessing factors which influence age at natural menopause should consider these issues.

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